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AIDS: AMYL-NITRITE USE AS A FACTOR

(A PROPOSED ANALYTIC CASE-CONTROL STUDY)

Donald James Yousey, B.A., R.N.
The University of Texas
Health Science Center at Houston
School of Public Health, 1984

Supervising Professor: Benjamin Bradshaw

A study design is proposed to test the hypothesis that amyl-nitrite use by homosexual males increases their risk of contracting AIDS. The need for further research in this area is based on the assessment that faulty comparison group selection in previous studies may have led to a conservative estimate of the importance of this factor.

Following the proposed study design, 81 AIDS patients would be compared in regards to their use of amyl-nitrite inhalant with 81 controls selected from a politically based homosexual group. The use of a politically based homosexual group as a source of controls is proposed as they are more representative of the general homosexual population than those used in previous studies. Use of such a group would then give a more accurate estimate of the importance of amyl-nitrite in the risk of contracting AIDS. Those individuals with a history of intravenous drug abuse, diagnosis of hemophillia or those claiming Haiti as their country of origin will be excluded. The case and comparison groups will be matched on number of sexual partners per month, use of bath houses for homosexuals and age. The information to make these exclusions and matchings will be collected during interviews with interviewers specially trained in dealing with sensitive material. Both interviewers and participants will be blinded concerning the specific underlying hypothesis of the study.

Collected data will be set up in two-by-two tables and Chi-square analysis will be applied. Two types of comparisons will be performed. First, the number of AIDS cases admitting to amyl-nitrite use will be compared with the number of controls with similar responses. The second approach will compare the number of respondents in each category with the number of times they used amyl-nitrite in the year prior to participation in the study or date of diagnosis. Each comparison will be considered significant if a p-value of .05 is exceeded by their respective Chi-square analysis.

AFIT/CI/NR 84-80T

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AUTHOR: Donald James Yousey

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( ) a. YES ( ) b. NO

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AIDS: AMYL-NITRITE USE AS A FACTOR

(A PROPOSED ANALYTIC CASE-CONTROL STUDY)

By

DONALD JAMES YOUSEY, B.A., R.N.

APPROVED:

Benjamin S. Bradshaw

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AIDS: AMYL-NITRITE USE AS A FACTOR

(A PROPOSED ANALYTIC CASE-CONTROL STUDY)

by

DONALD JAMES YOUSEY, B.A., R.N.

PROJECT

Presented to the Faculty of The University of Texas

Health Science Center at Houston

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF PUBLIC HEALTH
Houston, Texas
June 1984

For My Wife, Carol,

Without whose support, love and urging this proposal could not have been completed.

Table of Contents

ACKNOWLEDGEMENTS

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A special thanks to my wife, Carol Yousey, for helping to decipher my illegible notes, and editing and typing this proposal.

Finally, thanks to my children for understanding why I was not always as available as I would have liked.

Submitted: May 25, 1984

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Introduction

As of September 1983, approximately 2,260 cases of Acquired Immune Deficiency Syndrome (AIDS) had been identified. These cases had resulted in 917 deaths. The basic characteristics of the population affected by AIDS are as follows: "71% are men with homosexual or bisexual orientation; 17% (including 51% of the women affected) have used intravenous (IV) drugs; and 1% are hemophiliacs. Of the other 11% of cases means of disease contact is less clear, but in none of these cases does casual contact appear to have been involved" (Stein, 1980, pg.465). Although no specific cause has been identified at present, several etiologic causes have been suggested. Theories range from proposing that an unidentified agent is causing AIDS to suggesting that numerous and simultaneous contacts with immunity lowering agents (e.g. Cytomegalovirus (CMV), sperm in the blood stream, etc.) lead to the disease (Sonnabend, 1983, pg.2371-72). Although none of these theories have been proven, several behavioral factors have been identified as being positively associated with the risk of contracting AIDS. Such behaviors include: increased sexual activity among homosexuals (more than 1,100 different sexual partners per lifetime) (Marx, 1982, pg.618), passive anal intercourse (Sonnabend, 1983, pg.2371), intravenous drug abuse (Marx, 1982, pg.618), and inhalant drug abuse (Macek, 1982, pg.1425). Additionally, medical use of blood products and certain age groups have also been identified as risk factors (Stein, 1980, pg.466).

Just how significant the rise in risk is for each factor is not known in all cases. For example, in one study increased sexual activity was shown to be significant, but the rate of passive anal intercourse was not (Darrow, 1983, pg.160). One area in which questionable association has been suggested and in which more work is needed is the use of inhalant drugs such amyl-nitrite. These drugs are frequently used by homosexuals to intensify their sexual experiences and are thought to be both immunosuppresant and carcinogenic (Macek, 1982, pg.1425).

The Problem:

Reports of the association between the use of amyl-nitrite by male homosexuals and AIDS have been inconclusive. A hypothesis that has been proposed is that amyl-nitrite reacts with "amines and amides (amino acids, peptides, proteins, and metabolic products) to form N-nitrosamines and N-nitrosamites which are known to be mutagenic, carcinogenic and teratogenic" (Jorgensen, 1982, pg.894) thus leading to Kaposi's sarcoma. Results from another study suggest that amyl-nitrite may be immunosuppressive in the setting of repeated viral antigen stimulation. There was evidence of immunosuppression when amyl-nitrite was used during chronic Cytomegalovirus infections but immunosuppression was lacking when such infections occurred alone (Goedert, 1982, pg.415). In still another study of factors which might be associated with AIDS, nitrite inhalants were used by both cases and controls, but the lifetime exposure to nitrites was greater for cases than for controls (Jaffe, 1983, pg.147).

While these studies demonstrate a moderate positive association between the use of amyl-nitrite and an increased risk of contracting AIDS, some further questions have arisen. If the suggested positive association is true, why is there not a similar outbreak of AIDS in London where the use of amyl-nitrite is also quite common amongst homosexuals (McManus, 1982, pg.503)? Answering this particular question is not the goal of this proposal. A more tractable question that will be addressed by this study can

be based on a closer scrutiny of the earlier mentioned studies. In those studies, the controls were generally selected from homosexual volunteers (Goedert, 1982, pg.413), unspecified medical clinics (McManus, 1982, pg.503), or clinics for sexually transmitted diseases (Jaffe, 1983, pg.145). Are these individuals truly representative of the whole U.S. homosexual population? If not, could this have caused some distortion of the estimate of association of amyl-nitrite use to the risk of contracting AIDS? If AIDS victims are not representative of the U.S. homosexual population as suggested by the National Gay Task Force (Curran, 1983, pg.569) and the controls used in earlier studies are more like AIDS victims than the general population at risk, then the previous measurements of the positive association of amyl-nitrite use would indeed tend to be conservative. This could cause us to underrate the importance of such inhalant use and the magnitude of its role in the etiology of AIDS. Further, if members of the Gay Task Force or Gay Coalition are more representative of the general U.S. homosexual population and such a group was sampled to form a comparison group in a retrospective case-control study, a more realistic measurement of the association of amyl-nitrite use to the risk of contracting AIDS should be obtained. If, as I suggest, previous attempts to estimate this association have been biased to produce a conservative figure, new studies should be undertaken to produce a more accurate estimate of the association value. Almost every report surveyed by the author indicated a need for further

research to determine the factors that are associated with the occurrence of AIDS (Groopman, 1983, pg.576).

The following question is proposed by this study, "Is amyl-nitrite use by homosexual men positively associated with the contracting of AIDS?" Since the other previously mentioned life style factors (e.g. number of different sexual partners, use of bath houses to meet sexual contacts, and certain age groups) have been shown to have a positive association with the risk of getting AIDS, this design for an analytical retrospective case-control study will attempt to balance the cases and comparison group members for these factors to minimize confounding. Details on proposed techniques to accomplish the balancing will be presented in the methods section. Those abusing intravenous drugs, Haitians and hemophiliacs would not be included in the study. The rationale behind the approach for the proposed study is, if the two populations (i.e. case and comparison groups) are alike on other known associated factors, any differences in the use of amyl-nitrite between the two groups will indicate an association with the drug's use. My hypothesis is that a positive association exists.

Accurately identifying and estimating the potential risk of any factor (such as amyl-nitrite use) associated with AIDS permits the medical field to give behavioral guidance to the population in jeopardy, thus helping potential AIDS victims reduce their risk even before a specific causative agent or cure is identified. In the words of James Curran, M.D., head of the

CDC's task force, "We don't need to find the cause to inform people that they are at risk." However to give accurate advice about risk and what behaviors create risk, we need an accurate estimate of the association of each identified factor.

Operational Definitions of Variables:

"Before a hypothesis can be tested the investigator must operationaly define the variables stated in the hypothesis" (Zucker-Franklin, 1983, pg.111). To portray accurately the way each term will be used in the study, the specific measurement or assessment parameter proposed should be included in the definition. Following are the variables that the study will attempt to measure or match for:

1. "Use of amyl-nitrite" - subjects will be asked to estimate monthly frequency of use and span of use (i.e. how many years and months they have used this substance). Those admitting to usage for a period of three months or longer will be considered positive for usage.

2. AIDS cases will be: Homosexual men between the ages of 15 and 59 at the time of diagnosis who:

A. Have biopsy-proven Kaposi's sarcoma,

B. Have Pneumocystis pneumonia, or

C. Both

These are the two most common occurring symptoms of AIDS; 30% having Kaposi's sarcoma; 51% having Pneumocystis carini; and 7% having both (Allen, 1982, pg.1718). Thus using patients with these symptoms includes 70 to 80% of those diagnosed. Additionally, accepting only the most common presenting clinical features insures against non-representative cases being included. Those patients above the age of 60 with Kaposi's sarcoma will

not be included as this is the age ordinarily susceptible to the sarcoma. To include these men would confound the study, making inferences concerning risk to homosexuals less powerful. Additionally, men with known predisposing risk factors for either Kaposi's sarcoma or pneumocystis pneumonia (i.e. other malignancies or immunosuppressive drug therapy) will also be excluded (Groopmen, 1983, pg.145).

3. "Homosexual men" will be designated as those (case and controls) who have self identified themselves as having had sexual contact with one or more men in the year prior to diagnosis or participation in the study (Groopman, 1983, pg.145).

4. "Number of sexual partners per month" will be specified as the average number of different sexual partners per month in the year previous to diagnosis or participation in the study. Respondents with multiple sexual contacts with one person will be asked to count this as one contact.

5. "Use of bath houses to meet sexual partners" will be accepted as positive if respondents estimate that behavior as three or more times per year for the two years before diagnosis or participation in the study.

6. "Ages": AIDS cases will be asked to give month and year of diagnosis. Control group participants will be asked to give their age at the time of participation in the study interview. Both groups will be asked to give birth dates.

7. "Intravenous Drug Abusers" will be considered to be anyone who admits to using a non-prescription intravenous drug

during the two year period immediately preceeding being interviewed or diagnosed.

8. "Haitians" will be those respondents reporting themselves as being of Haitian birth.

9. "Hemophiliacs" will be defined as those who answer positively to such medical diagnosis during the interview.

Those definitions footnoted are as used by previous researchers. Those not footnoted, are descriptions of how those terms will be used in this particular study since specific operational definitions were not available for previous studies.

Methods and Procedures:

As stated, the goal is to obtain a more accurate measurement of the strength of association between amyl-nitrite use and the occurrence of AIDS in homosexual men. The use of an analytic case-control study as used by earlier researchers appears appropriate, but a more representative comparison group needs to be chosen. Additional objectives are to include a balancing of case and comparison populations on other factors that might have a confounding effect on the outcome of the study. Since we are dealing with men only, sex as a factor may be ignored. Three other pre-diagnosis factors that have been identified as being positively associated with the risk of contracting AIDS are:

1. Number of different sexual partners per month,
2. Use of bath houses to meet sexual contacts,
3. Certain age groups (47% of AIDS victims are between 30-39 years of age).

The appearance of this high risk in the 30 to 39 year old age group most probably is two fold. First, the large number of sexual partners per lifetime would take a long time to be achieved. Thus, younger homosexuals have not been at risk as many person years as those in this age category. The second aspect of this phenomena is concerned with the decrease in numbers of AIDS cases after age 39. This may well be explained by the fact that these individuals matured at a time when society was much less acceptant of homosexuals than it is presently and those presently comprising

the 30 to 39 year old age group have led more conservative life styles. This would decrease their risk of contracting AIDS. If this explanation regarding the fall off in incidence after age 39 is true, we would expect an increase in the incidence in the discussed age group as the cohort now occupying it ages and is replaced by the less conservative, younger homosexuals.

Since intravenous drug abusers, Haitians and hemophiliacs will be excluded, risk of confounding from these factors will be removed. This will be done by noting interview responses concerning drug abuse, country of origin and the possibility of being hemophiliac. Care must be taken to assure participants that drug use information will in no way jeopardize them with legal authorities, or a falsely low positive response rate can be expected. I propose to collect data on the AIDS cases population, tabulate averages for noted behaviors and then use comparison group members whose responses are similar on the controlled variables. For number of sexual partners per month, any comparison respondent that gives an answer plus or minus one standard deviation of the cases' overall mean will be considered comparable. As part of the proposed balancing, accepted respondents will be limited to between the age of 30 and 39, thus including the greatest number at risk and balancing out the effects of age association. Since certain age groups appear to be more at risk than others, by balancing in age category both cases and controls will be at similar risk secondary to

the age factor. The information collected will be through interviews. Formulation of appropriate interview questions will be part of the study. Once approval to continue is obtained, written communications will be initiated with other researchers concerned with the AIDS problem to request a copy of the questionnaires used by them so that aspects of their questionnaire can be incorporated in the proposed survey. Use will also be made of standardized questionnaires employed for obtaining information about sexual contacts of venereal disease patients.

AIDS Cases:

As many cases of AIDS as possible would be contacted through a major treatment facility in New York City. This area is chosen because of the high concentration of known cases located there (Allen, 1983, pg.467).

Approval to interview AIDS patients as prospective cases for this study will have to be obtained from the specific facility selected before any information can be collected. The basic underlying need for research will be communicated to the facility directors, but actual underlying theory should not be revealed. This is to limit the chances of respondents being informed (knowingly or otherwise) of this theory and thus biasing their answers. Those patients that agree to participate at the first interview will then be scheduled for a longer, in depth interview. While the patients will be queried about personal data, sexual behavior and drug use at this second interview, their identity will not be recorded on the actual interview questionnaire. The questionnaire will instead be coded to protect their privacy. Data generated by the survey would be used for general population description and for analysis, but individual responses would not be used (to protect further the privacy of respondents).

The treatment staff would be asked to supply a list of their AIDS patients who fit the criteria given in the operational definition section so they can be queried about participating

in the study. Homosexual men will be designated as those who have had sexual contact with one or more men in the year prior to their illness. This criterion for acceptance into the study population was previously used in the cited study and appears appropriate for use here (Groopman, 1983, pg.145). Additionally, using the same criterion will help limit confounding by making this population similar to previously studied populations. That is, if this study is similar to previous studies in all aspects except the choice of the control group, then any changes in the outcome could most likely be attributed to that factor. The project goal is to obtain 81 acceptable interview questionnaires for both groups, but all respondents meeting criterion will be accepted (Schlesselman, 1974, pg.383). The sample size was determined using Mr. Schlesselman's suggested formula with the following particulars: Alpha .05, Beta .10, and a p-value of .05. Informed consent forms will be attached to each interview questionnaire for participants' signatures, but will be detached from the actual questionnaires immediately upon receipt to further protect the privacy of the AIDS patients during handling of this personally sensitive information. Informed consent forms and survey questionnaires will then be coded for later rematching if necessary for follow-up controls. See appendix "A" for an example of the informed consent form.

Use of previously collected information was considered for financial reasons and ease of access, but was decided against. Although collecting new information will entail much

extra labor and expense, it is considered necessary because of the time element. That is, there has been a change in the number of cases of AIDS being reported since previous studies were completed. According to a recent report (MMWR, April 6, 1984) the exponential growth in the number of cases being reported in the literature appears to have slowed for the time being (MMWR, 1984, pg.172). This change may be due to education of those at risk secondary to the Public Health Service's guidelines on factors that are positively associated with AIDS and the resultant alteration of behaviors. The actual cause for this change is not known at this time and any explanations are only speculation. But, if the suggested cause presented here is true, comparing previous surveys of behavioral levels with present activity might well spuriously magnify the strengths of association.

Comparison Group:

As stated earlier, previous studies may have erroneously underrated the strength of association of amyl-nitrite use to the occurrence of AIDS because their comparison groups were more like the cases than the general homosexual population. To correct this error, I propose to approach a group of homosexual men not connected to any medical clinic or treatment facility. Instead, the author would contact a New York based homosexual organization (Gay Task Force, Gay Coalition, etc.) and ask them to query their total membership about participation in such a research survey. If agreement to participate is obtained, and the importance of such research is accepted by the members, the need for accurate responses in the interview must then be stressed. The interview questionnaire used with this group would be identical to that filled out for the AIDS cases except that it would be clearly entitled "Control Group Interview Questionnaire". To avoid potential bias, participants cannot be informed of the underlying hypothesis or possible bias from previous poorly chosen comparison groups, as this would likely lead them to slant their answers and bias the outcome of the study. Controls would also be balanced with the case group members according to age, number of different sexual partners per month and use of bath houses to make sexual contacts (as described earlier). Thus a much larger number of potential controls would need to be interviewed to

ensure that a number equal to that in the case group is obtained. Intravenous drug abusers who have used drugs in the past two years will be excluded from this group as well. Those answering positively for diagnosis of hemophilia will also be excluded from the control group.

The same guarantees of anonymity and protection of individual privacy given the AIDS patients must be given to participants in the control group. The protection of interview questionnaires and the generalization of data to population figures (versus individual data) will afford this protection.

Many steps to guard against confounding have already been described, but at least one more area needs to be covered. That is the need to ensure that cases of AIDS do not get into the control group by accident and thus bias the study results. Since, there is a long (one year plus) latency period (Check, 1983, pg.568) and no accurate screening test presently available, this poses what appears to be a difficult problem. In fact, if we try to screen out those who may be in the latency period, but not yet presenting symptoms, the problem is insurmountable with the current level of knowledge of AIDS. One way to overcome this obstacle is by waiting two years before compiling the final statistical analysis. By waiting two years and then querying the accepted respondents about their physical condition, those previously placed in the control group who later were diagnosed as having AIDS could be removed from the control group and thus ensure as much as possible that no latent AIDS victims

would erroneously be included in the control group. This is further justification for interviewing more controls than cases. Furthermore, if some controls turned out to have AIDS, they could be shifted into the case side in the final analysis. While this would ensure as much as possible that the control group is kept uncontaminated, the loss of time may prove to be more costly (as far as usefullness of the study goes) than the amount of accuracy gained. Another possible approach might be to estimate statistically the chances of the control group being contaminated if such a precaution is not taken. If this is low enough (say less than five percent), then it might be more prudent to continue with the study analysis as soon as possible so that the needed information is obtained sooner. Actually, doing both and releasing tentative results is probably the most prudent course.

Data Collection:

As stated earlier, data will be collected by interviewer administered questionnaires. The use of anonymous survey questionnaires was strongly considered, but one study of that technique showed only a 20% response rate (Marquis, 1977, pg.6). The chances that the respondents would not comprise a representative sample would be too great. Thus, the more expensive and time consuming but hopefully more accurate interviewer administered questionnaire was chosen. Even with this procedure, an unknown percentage of persons would refuse to participate. Therefore, it will be necessary to include questions about basic characteristics (age, race, national origin, etc.) in order to estimate the degree to which nonparticipants differ from participants.

Dealing with such personal information as this study requires also calls for a more controlled collection device than an anonymous survey. Further, such information calls for specially trained personnel to administer the interviews. If the questions are administered in too negative a fashion, the participants might be led to underestimate their activity levels. On the other hand, leading participants to overestimate their activity levels will cause a bias in the other direction. Thus, extremely skillful interviewers are called for. To recruit and train individuals especially for this study would be both time consuming and expensive. Since most local public health departments

already employ personnel trained in dealing with such sensitive material in their venereal disease clinics, this seems to be both an opportune and appropriate area for recruitment of the needed interviewers. A large health department such as that in New York City would be an excellent source for interviewers. Informing the interviewers that a comparison of behaviors of the two groups is the basis of the study without actually giving them the specific underlying hypothesis should provide adequate blinding to safeguard against their biasing the participants' responses. Two interviewers would be sufficient to collect the data for this study.

At the time of the interviews, the participants will be asked to sign an informed consent form (see Appendix "A"). Participants will be provided a personal copy of the informed consent form that will contain the author's telephone number should they need to contact him with any questions that might arise. It is at the time of the signing of the informed consent form that participants will be instructed about planned steps to protect their privacy in regards to answers given during the ensuing interview. Obviously, the wording of the form would be consistent with that customarily used by the institution under whose auspices the study is conducted, and might be more or less detailed.

Returning to the discussion of the interviewers, inter- and intra-interviewer variation needs some attention. The first is concerned with one interviewer dealing with different

participants in widely varying manners that might in some way cause them (the participants) to bias their responses. The second would be the variation in responses that two different interviewers would get if they interviewed the same participant. Hopefully, the responses would be essentially the same in both instances or some bias might creep into the study. By identifying two participants to be interviewed by the same interviewer twice without his knowledge and two others to be interviewed by separate interviewers, the results could be compared and the two risks of bias could be evaluated and discussed when the study results are written up. By ensuring that each interviewer interfaces with a similar number of cases and controls, an influencing would hopefully effect the two groups in a like manner.

While the actual design of the interview questionnaire form would be part of this proposal if approval and funding were obtained, a problem arises at this point that was mentioned briefly earlier. That problem is the need to conceal the underlying hypothesis of previous studies being biased by non-representative comparison groups. If we query the AIDS cases and comparison group members about amyl-nitrite use only, they would most likely be able to ascertain the reason for the study and then bias their responses. Additionally, other information is necessary to do the needed balancing described earlier and any follow-up deemed necessary. Other factors and personal information collected might possibly but not necessarily

include or be limited to the following:

1. Age (date of birth)
2. Sexual preference and estimate of contacts in the past two years
3. Race or Ethnicity (Country of origin)
4. Whether diagnosed as hemophiliac
5. Estimate of use of non-prescription drugs for the past two years
   a. Marijuana - frequency of use
   b. I.V. drugs - frequency of use
   c. Amyl-nitrite inhalant - frequency of use
6. Estimate of yearly income
7. Education level
8. Estimate of bath house usage to make sexual contacts
9. Incidence of sexually transmitted diseases and hepatitis; types and frequency
10. Estimate of alcohol use; frequency and amounts per sitting
11. Estimate of number of different sexual partners for:
    a. the past month
    b. the past year
    c. lifetime
12. Preferred sexual practices (rectal intercourse, fellatio,"fisting", etc.), preferred role (insertor, insertee), frequency of practices.
13. Willingness to be contacted for follow-up if necessary. Must be made aware of need to divulge address and/or phone number if answer is yes.

In addition to the specific question areas described in the previous paragraph, there are other particulars regarding the interview questionnaire that are already set. The three main components of the questionnaire (i.e. content, question form and level of data) will probably remain as follows:

1. Content: will be limited to identifying information (to be kept on informed consent forms), behaviorial patterns and demographic data.
2. Question format: will be multiple choice wherever possible with open ended questions used no more than absolutely necessary.

3. Level of Data: will be factual rather than attitudinal.

The actual construction of question items will follow those rules suggested by Stein in Anatomy of Research in Allied Health (Stein, 1980, pg.135). In constructing the question items, Stein states that researchers should "be aware of the following:

1. The choices available to the subjects should be exhaustive. On some items a place for "other, please specify" should be provided.
2. The choices should be mutually exclusive.
3. The items should be unambiaous and precise. A pilot study testing the reliability of items is essential.
4. Items should ask only one question. Avoid double-barreled questions.
5. The respondent should have enough information to answer the item.
6. The researcher should have a rationale for each item asked. The questionnaire should not be padded with irrelevant items.
7. Negative questions should be avoided.
8. Leading questions that force a response should be omitted. The respondents should not be in a position to give expected answers or opinions" (Stein, 1980, pg.137).

The "pilot survey" appropriately should be administered to a small number of persons, specifically members of a homosexual organization. This would assist in the wording and structuring of the questionnaire for best response.

After collection and coding, questionnaires would be stored securely and separately from the informed consent forms as discussed previously. The only connection between the two being the code number.

In addition to using a procedurally correct approach

to the construction of the interview questionnaire, there is one other area that should be dealt with at this time. That area concerns testing the accuracy of responses to the question items presented. One way to approach this is to ask the same question twice during the same interview but in different ways. This might be done by querying a participant about whether he uses non-prescription drugs and then later asking about use of several specific non-prescription drugs. If the respondent answers negatively on the first question, but positively on one of the later items, then one might want to look closer at the reason for the discrepancy. If the problem is just a misunderstanding, this might easily be dealt with by reconstructing the problem item. If, on the other hand, the discrepancy is due to defensiveness or bravado, there might be a problem with the accuracy of most data from this respondent. If a similar situation were found with other respondents, the accuracy of the whole study might be in jeopardy. The proper development and administration of the questionaire should minimize the chances of this occurring.

It is obvious that there are some problems with attempting to guarantee reliability and validity of data collected in the described manner. Answers about personal behaviors spanning an entire year based on memory are open to errors secondary to memory distortion, subjective interpretation of questions presented and defensive underestimating. The importance of protecting participants' right to privacy make such risks of

loss of accuracy in the collection of the data necessary. It is hoped that if memory problems, subjectiveness, or defensiveness do play a part in how respondents answer their questionnaires, that it will affect both the cases and the control group in a similar fashion and influence their answers in the same direction. If not, this may well be a source of bias.

Still another crucial issue that needs some explanation is the need to deal with the sensitivity of the information being surveyed. Some effort must be made to explain to respondents the necessity for accurate replies to such personal questions. The extreme importance of not overestimating or underestimating the frequency of specified behaviors must be stressed by the interviewer while ensuring the participants that all precautions will be taken to guarantee their anonymity and privacy. A specific explanation of the importance of accurate responses and planned precautions to protect anonymity of respondents on the informed consent form seems to be the best approach to this problem as discussed in an earlier section.

Projected Analysis of Data:

The purpose of this proposal is to answer the question of whether there is a significant association between amyl-nitrite use in homosexual men and their risk of contracting AIDS. Each respondent's choice of whether to use amyl-nitrite is ultimately an individual one and thus independent of other respondents' choices in the same matter. (This is not to say, however, that other persons' use of amyl-nitrite would not influence an individual's choice to use or not to use the drug.) For the purpose of this study, amyl-nitrite use between cases and the control group will be compared in two ways.

First, the proportion of respondents in the AIDS category who admit to amyl-nitrite use will be compared with the proportion of respondents in the comparison group who admit to previously using amyl-nitrite (usage for a period of three months or longer will be considered positive). These numbers will be set up in a two-by-two table and a chi square analysis will be performed. Significance will be set at the .05 level. If the difference appears to be significant at this level, an Odds Ratio will be determined. Since AIDS is a rare disease the Odds Ratio will be will be used to estimate the relative risk of the possibility of contracting AIDS between the two groups.

The second approach will be to set up a two-by-two table comparing the numbers of respondents in each category with the number of times they used amyl-nitrite in the year prior

to diagnosis (cases) and the year before completing the questionnaire (comparison group). Again, a chi square analysis of significance at the .05 level will be applied (as will the Odds Ratio and relative risk).

Similar tests of those factors that were surveyed but not balanced for might also prove useful since the data will be readily available without extra effort or financial burden. These additional tests may well have to be reported separately so as not to cloud the main issue of testing the association of amyl-nitrite use to the risk of contracting AIDS.

If a significant association is shown to exist between the risk of contracting AIDS and one or more of these other factors, a trend analysis will be done to see if there is some hidden connection between amyl-nitrite use and these other factors. If no trend is shown, we can assume that the association of amyl-nitrite use to AIDS is independent of these other factors. Whether there may be still other factors that are somehow connected with amyl-nitrite use is another matter that might be looked at in future research. If, on the other hand, the trend analysis does show a relationship between amyl-nitrite use and one or more of these other factors, the significance of this attempt at obtaining a more accurate measurement of the association between amyl-nitrite use and AIDS will still be questionable. At that juncture, it would become important to determine in what way the factors were related. Further research would be called for to determine

whether the observed associations were significant or just markers of some more important, but less visible factor. Since this particular research proposal is not intended to answer that question, a different project designed just for that purpose would be called for.

If this study does indeed show a significant positive association between amyl-nitrite use and AIDS, then this relationship will be important to the population at risk. Current Public Health Service guidelines do not include warning on this factor (U.S. Public Health Service Handout, 1983, pg.1) possibly because of a faulty estimate of its importance in the previously cited studies. However, this one study could not be immediately accepted as superior to those before it. Either further studies to replicate its findings or studies to obtain more information about the hypothesized association may be necessary. If the future studies support the findings of this proposed study, then the Public Health Service guidelines should be updated to reflect the new information.

It must be stated at this point that any problems with the statistical procedures proposed above will be dealt with through further consultation with a biostatistician. Since the author claims no expertise in statistics, all consultation and their sources will be well documented.

Time and Facilities Needed:

1. Time Schedule: (See Appendix "B" for Gantt Chart)

   January to March, 1985: Presentation of requests for proposal approval to specific treatment facility and homosexual organization in New York area.

   April to July, 1985: Formulation of interview questionnaires and printing (this includes printing of envelopes and informed consent forms). This period also includes contacting previous researchers to obtain copies of questionnaires used by them if necessary.

   August to October, 1985: Completion of interviews and signing of informed consent forms (includes coding and separate filing to protect participant anonymity).

   November to December, 1985: Preparation of data and carrying out of statistical procedures listed in analysis section of proposal.

   January to March, 1986: Construction of write-up results, conclusions and suggestions for further research if needed.

   July to October, 1987: Recontact control group members to ascertain health status and removal of any control group members diagnosed as having AIDS since completion of interview questionnaires. This information may be obtainable from the participating homosexual organization if recontact proves impossible.

2. Budget: (Needed goods, not financial figures)

A. Space: Researcher will use personal office space for design of proposal, drafting forms, letters, calculation of statistical procedures and drafting of results.

B. Personnel:

1. Author will complete majority of study drafting and statistical analysis personally.
2. Interviewers will be hired from a New York City Public Health Venereal Disease Clinic to conduct interviews with both AIDS cases and the comparison group.
3. Periodic consultation with Dr.'s Eifler and Scholl for statistical support is planned.
4. Continued consultation with Dr.'s Bradshaw and Werner concerning study design and implementation is expected.
5. Typing support is necessary for preparing of interview questionnaires, proposal production and results reporting.

C. Equipment:

Type:	Number:	Time Span Needed:
1. Desk	Two	Two years
2. Typewriter	Two	Two years
3. Calculator	One	Two years
4. Telephone	One	Two years

D. Supplies:

Type:	Amount:
1. Stationery	Approximately 2,000-3,000 sheets
2. Stamps	Approximately 350 stamps

D. Supplies (Continued)

Type:	Amount:
3. Envelopes	Approximately 350 count
4. Pens/Pencils	One dozen each

E. Travel: Three trips to the metropolitan New York area are projected. The first is a two week trip at the beginning of the study to hire interviewers and meet with respective contacts at the treatment center and homosexual comparison group organization. Another to deal with unforseen problems that might arise and one at the study termination to tie up loose ends are planned.

Summary:

While this study is being proposed to try to overcome the difficulty of selection bias that may have occurred in earlier studies, the question of whether using members of a politically active homosexual group may well be criticized in a similar fashion. There may be those who question that this group would be too conservative to be representative of the whole homosexual male population at risk. If the results of this study were to yield a positive association, then further descriptive studies of the homosexual population may be necessary to validate application of this particular study to the whole population at risk.

Another problem not yet discussed is the matter of sample size. Because of the rareness of the disease and the logistics of contacting AIDS victims, this study is limited to those in a single, high concentration geographical area. This will, in turn, have a limiting effect on the number of individuals in the samples drawn. If the study proves negative, one would want to look at sample size to ascertain if maybe that alone could have led to the findings. Further, might not larger sample sizes have provided positive results without any change in the ratios of responses to questions about the factor being studied?

While all these questions cannot be answered at this time, it is important to keep them in mind while constructing

the study design so conclusions are not drawn without giving full creedance to the many possible explanations for any results reached. Additonally, the problems do not negate the need for further studies to gain a clearer understanding about all the factors that are associated with the risk of contracting AIDS.

Appendix "A"

INFORMED CONSENT FORM: (Cases or Controls)

1. Proposed study: Attached is an interview questionnaire that is designed to obtain information about homosexual males who may be at risk of contracting Acquired Immunodeficiency Syndrome (AIDS). This interview questionraire will be completed by both identified patients and a number of individuals free of disease to measure their levels of activity in certain behaviors and to collect some particular background information. After this information has been collected, similarities and differences between the two groups surveyed will be drawn from the information submitted in the hopes of gaining more information about this terrible disease.

2. Protection of Privacy: Specific questions asked during the interview deal with sensitive personal information. Please be assured that if you agree to participate that:
   A. No negative inference is intended by any behavioral area surveyed.
   B. Steps will be taken to protect your right to privacy through:
      1. Coding of individual answer sheets
      2. Files containing names and other identifying information will be stored separately from the actual interview questionnaires. The only link will be by the code number.
      3. Information generated will be formulated in such a manner as to describe characteristics of the groups as a whole (versus individuals) thus making inferences about individuals by anyone not cleared for access to this material extremely difficult if not outright impossible. Individual responses will not be reported or released.

3. For the information obtained in this survey to be useful, it is paramount that your answers about your activities and levels of participation in the behaviors surveyed be as accurate as possible.

4. Possible Benefits of Study: The only personal benefit that individual respondents might gain from participation in this study is the feeling that they are contributing information that might lead to a better understanding of AIDS and those at risk to contracting AIDS. Beyond those participating in this research, however,the whole population at risk gains each time more information is obtained about this disease that may provide guidance about ways of limiting their personal risk to contracting AIDS.

5. Any questions that may remain unanswered by the previous information will be gladly answered by the researcher. Please feel free to contact researcher if necessary. Researcher is: Donald J. Yousey, Phone (512) 680-7797.

6. Participation in this study is completely voluntary. Refusal to participate will in no way reflect on those who choose to do so. Nor will a decision not to participate have any effect on an individual's treatment or benefits. Respondents maintain all rights to withdrawal or discontinuance of participation at any time without penalty or prejudice with respect to such matters as health care, education, employment, or compensation.

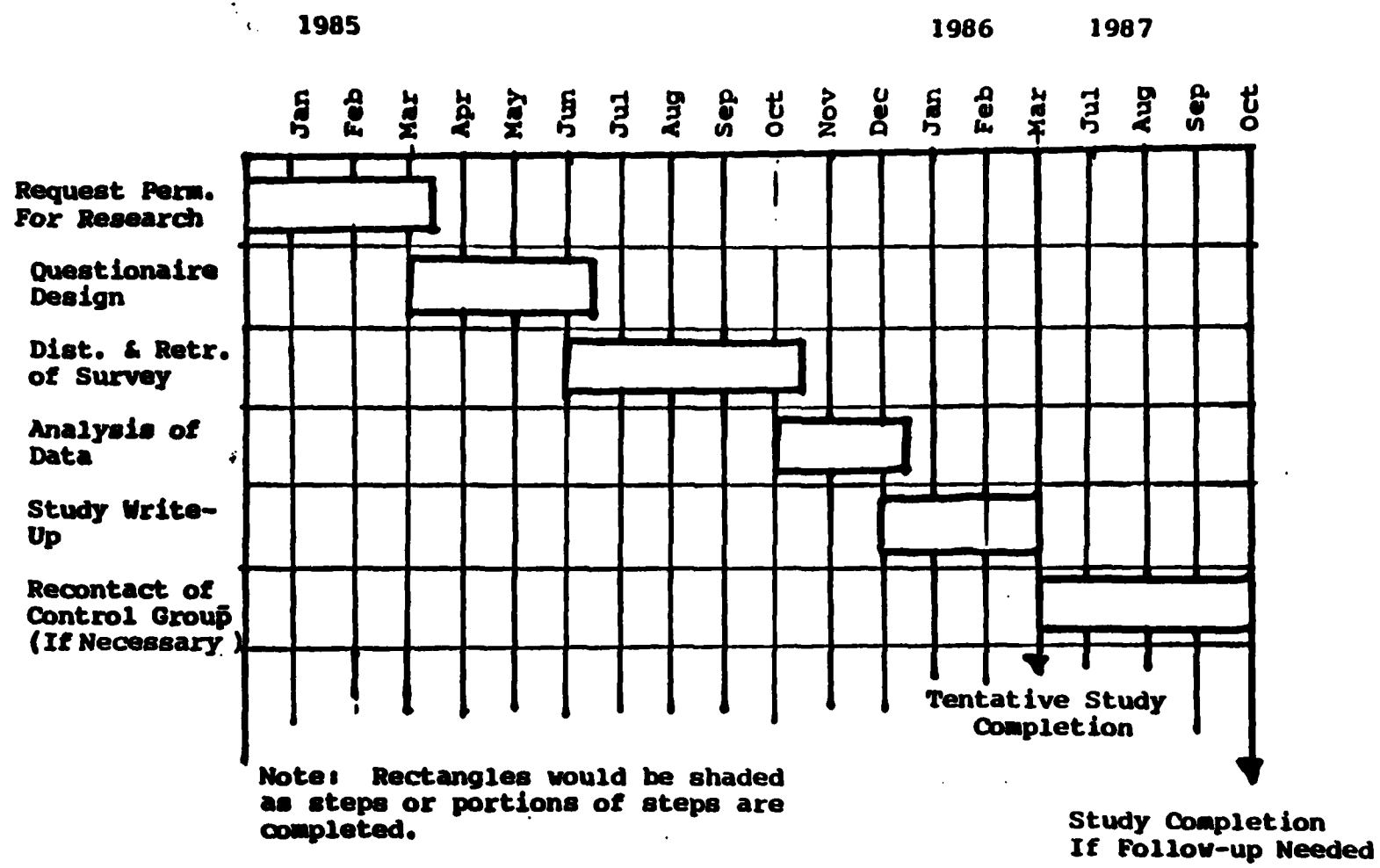
7. By signing this document, the undersigned states that he has read this informed consent form (a copy of which will be provided at the time of signature).

SIGNATURE: _____ DATE: _____

ADDRESS: _____

PHONE: _____

APPENDIX "B": Gantt Chart



Note: Rectangles would be shaded as steps or portions of steps are completed.

While consultation with a statistician is not reflected with a rectangle, the author expects to make such consultation throughout the entire study period.

References:

Abramson, J. H., Survey Methods in Community Medicine, New York: Churchill Livingstone, 1979.

Allen, Jeanne, Mellin, Grace, "The New Epidemic", American Journal of Nursing, November 1982.

Auerbach, David, M.D., "Epidemiologic Aspects of the Current Outbreak of Kaposi's Sarcoma and Opportunistic Infections", The New England Journal of Medicine, January 28, 1982.

Check, William, "Preventing AIDS Transmission: Should Donors Be Screened?", Journal of the American Medical Association, February 4, 1983.

Curran, James W., M.D., et al., "Acquired Immunodeficiency Associated with Blood Transfusions", The New England Journal of Medicine, January 12, 1983.

Darrow, William W., et al., "Passive Anal Intercourse as a Risk Factor", The Lancet, July 16, 1983.

"Facts About AIDS", U.S. Public Health Service Handout, August 1983, (No author given).

Fauci, Anthony S., M.D., et al., "Acquired Immunodeficiency Syndrome: Epidemiologic, Clinical, Immunologic, and Therapeutic Considerations", Annals of Internal Medicine, January 1984.

Gerety, Robert J., M.D., Ph.D., Tabor, Edward, M.D., "Newly Licensed Hepatitis B Vaccine", The Journal of the American Medical Association, February 11, 1983.

Gilmore, N. J., Ph.D., M.D., et al., "AIDS: Acquired Immunodeficiency Syndrome (Current Review)", Canadian Medical Association Journal, June 1, 1983.

Goedert, James J., et al., "Amyl-Nitrite May Alter T Lymphocytes in Homosexual Men", The Lancet, February 20, 1982.

Groopman, Jerome E., Gottlieb, Michael S., "AIDS: The Widening Gyre", Nature, June 16, 1983.

Handsfield, H. H., "Acquired Immunodeficiency in Homosexual Men", American Journal of Roentgenology, October 1982.

"Leads from the MMWR", The Journal of the American Medical Association, March 25, 1983, (No author given).

Jaffe, Harold W., M.D., et al., "National Case Control Study of Kaposi's Sarcoma and Pneumocystis Carinii Pneumonia in Homosexual Men", Annals of Internal Medicine, August 1983.

Jorgensen, Karl A., M.D., "Amyl-Nitrite and Kaposi's Sarcoma in Homosexual Men", The New England Journal of Medicine, September 30, 1982.

Macek, Catherine, "Acquired Immunodeficiency Syndrome Cause(s) Still Elusive", The Journal of the American Medical Association, September 24, 1982.

Macek, Catherine, "AIDS Transmission: What About Hepatitis B Vaccine?", The Journal of the American Medical Association, February 11, 1983.

Maddox, John, "Planning More Research on AIDS", Nature, June 2, 1983.

Marquis, M. Susan, Measurement Evaluation of the Health Insurance Study and Screening Interview, Santa Monica: Rand, 1977.

McManus, J. J., et al., "Amyl-Nitrite Use by Homosexuals", The Lancet, February 27, 1982.

Marx, Jean, "New Disease Baffles Medical Community", Science, August 13, 1982.

Marx, Jean, "Spread of AIDS Sparks New Health Concern", Science, February 7, 1983.

Oleske, James, M.D., MPH, et al., "Immune Deficiency Syndrome In children", The Journal of the American Medical Association, May 6, 1983.

Pape, Jean W., M.D., et al., "Characteristics of the Acquired Immunodeficiency Syndrome (AIDS) in Haiti", The New England Journal of Medicine, October 20, 1983.

Pearce, Richard B., "Intestinal Protozoal Infections and AIDS", The Lancet, July 2, 1983.

Schlesselman, James J., "Sample Size Requirements in Cohort and Case-Control Studies of Disease", American Journal of Epidemiology, June, 1974.

Sonnabend, Joseph, M.D., MRCP, et al., "Acquired Immunodeficiency Syndrom, Opportunistic Infections, and Malignancies in Male Homosexuals", The Journal Of the American Medical Association, May 6, 1983.

Stein, Franklin, Anatomy of Research in Allied Health, New York: Schenkman Publishing Company, 1980.

"Update: Acquired Immunodeficiency Syndrome (AIDS) - United States", MMWR, September 9, 1983, (No author given).

Viera, Jeffrey, M.D., et al., "Acquired Immune Deficiency In Haitians", The New England Journal of Medicine, January 20, 1983.

Zucker-Franklin, Dorothea, M.D., "Looking For the Cause of AIDS", The New England Journal of Medicine, April 7, 1983.